(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 August 2001 (30.08.2001)

PCT

(10) International Publication Number
WO 01/62749 A1

(51) International Patent Classification[7]: C07D 295/18, A61K 31/495

(21) International Application Number: PCT/US01/05510

(22) International Filing Date: 22 February 2001 (22.02.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/184,206 22 February 2000 (22.02.2000) US

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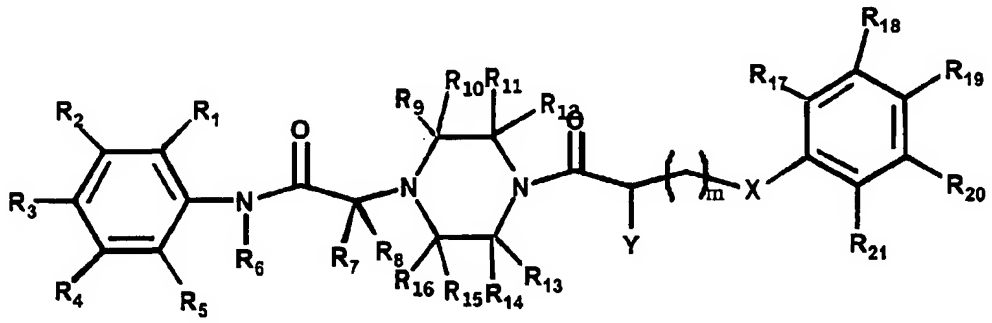
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SUBSTITUTED PIPERAZINE COMPOUNDS



(I)

(57) Abstract: Novel compounds of general formula (I), and pharmaceutically acceptable acid addition salts thereof, wherein the compounds are useful in therapy to protect skeletal muscles against damage resulting from trauma or to protect skeletal muscles subsequent to muscle or systemic diseases such as intermittent claudication, to treat shock conditions, to preserve donor tissue and organs used in transplants, in the treatment of cardiovascular diseases including atrial and ventricular arrhythmias, Prinzmetal's (variant) angina, stable angina, and exercise induced angina, congestive heart disease, and myocardial infarction.

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SUBSTITUTED PIPERAZINE COMPOUNDS

BACKGROUND OF THE INVENTION

This application claims priority to U.S. Patent Application No. 60/184206 filed on February 22, 2000, the specification of which is incorporated herein by reference.

1. Field of the Invention

The present invention is concerned with substituted piperazine compounds, therapeutic dosage forms including one or more of the compounds, and methods for treating diseases in mammals, and in particular, in a human in a therapy selected from the group including protecting skeletal muscles against damage resulting from trauma, protecting skeletal muscles subsequent to muscle or systemic diseases such as intermittent claudication, to treat shock conditions, to preserve donor tissue and organs used in transplants, and to treat cardiovascular diseases including atrial and ventricular arrhythmias, Prinzmetal's (variant) angina, stable angina, and exercise induced angina, congestive heart disease, and myocardial infarction.

2. Description of the Art

U.S Patent No. 4,567,264, the specification of which is incorporated herein by reference, discloses a class of substituted piperazine compounds that includes a compound known as ranolazine, (±)-N- (2,6-dimethylphenyl)-4-[2-hydroxy-3- (2-methoxyphenoxy)-propyl]-1-piperazineacetamide, and its pharmaceutically acceptable salts, and their use in the treatment of cardiovascular diseases, including arrhythmias, variant and exercise-induced angina, and myocardial infarction.

U.S. Patent No. 5,506,229, which is incorporated herein by reference, discloses the use of ranolazine and its pharmaceutically acceptable salts and esters for the treatment of tissues experiencing a physical or chemical insult, including cardioplegia, hypoxic or reperfusion injury to cardiac or skeletal muscle or brain tissue, and for use in transplants. In particular, ranolazine is particularly useful for treating arrhythmias, variant and exercise-induced angina, and myocardial infarction by partially inhibiting cardiac fatty acid oxidation. Conventional oral and parenteral ranolazine formulations are disclosed, including controlled release formulations. In particular, Example 7D of U.S. Patent No. 5,506,229 describes a controlled release formulation in capsule form comprising microspheres of ranolazine and microcrystalline cellulose coated with release controlling polymers.

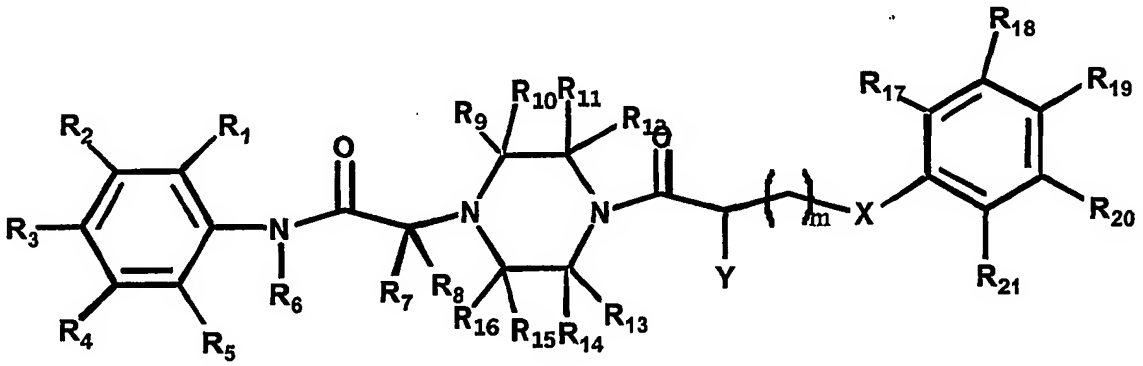
Despite the important discovery that ranolazine is a very useful cardiac therapeutic agent, there remains a need for compounds that are partial fatty acid oxidation inhibitors that have a half-life greater than ranolazine and that have activities as least similar to ranolazine.

SUMMARY OF THE INVENTION

This invention includes novel substituted piperazine compounds that are partial fatty acid oxidation inhibitors with good therapeutic half-lives.

This invention also includes novel substituted piperazine compounds that can be administered to a mammal to protect skeletal muscles against damage resulting from trauma, to protecting skeletal muscles subsequent to muscle or systemic diseases such as intermittent claudication, to treat shock conditions, to preserve donor tissue and organs used in transplants, and to treat cardiovascular diseases including atrial and ventricular arrhythmias, Prinzmetal's (variant) angina, stable angina, and exercise induced angina, congestive heart disease, and myocardial infarction.

This invention includes a class of substituted piperazine compounds having the following formula:



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wherein X = -O- or $(CH_2)_n$; Y = -OH or hydrogen; n = 0 or 1; m = 0 or 1;

R_1, R_2, R_3, R_4 and R_5 are each independently selected from the group consisting of hydrogen, halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, SO_2R_{22}, $SO_2N(R_{23})_2$, $NR_{23}CO_2R_{22}$, $NR_{23}CON(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, $NR_{23}SO_2R_{22}$, $C_{1\text{-}15}$ alkyl, $C_{2\text{-}15}$ alkenyl, $C_{2\text{-}15}$ alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl substituent are optionally substituted with 1 substituent selected from the group consisting of halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, and SO_2R_{22};

R_6, R_7 and R_8 each independently selected from the group consisting of hydrogen or $C_{1\text{-}15}$ alkyl;

R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of hydrogen, CO_2R_{23}, $CON(R_{23})_2$, C_{1-4} alkyl, or aryl wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, CF_3, CN, OR_{23}, $N(R_{23})_2$, CO_2R_{23}, $CON(R_{23})_2$ or aryl, wherein R_9 and R_{10} may together form a carbonyl, or R_{11} and R_{12} may together form a carbonyl, or R_{13} and R_{14} may together form a carbonyl, or R_{15} and R_{16} may together form a carbonyl wherein R_{11} and R_{13} or R_9 and R_{15} or R_9 and R_{11} or R_{11} and R_{15} or R_9 and R_{13} may join together to form a bridging ring system wherein the two R groups together comprise of from 1 to 4 carbon atoms and wherein R_9 and R_{10} or R_{11} and R_{12} or R_{13} and R_{14} or R_{15} and R_{16} may join to form a bridging ring system wherein the two R groups together comprise of from 1 to 5 carbon atoms;

R_{17}, R_{18}, R_{19}, R_{20}, and R_{21} are each independently selected from the group consisting of hydrogen, halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, SO_2R_{22}, $SO_2N(R_{23})_2$, $NR_{23}CO_2R_{22}$, $NR_{23}CON(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, $NR_{23}SO_2R_{22}$, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl substituent are optionally substituted with 1 substituent selected from the group consisting of halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, and SO_2R_{22};

R_{22} is selected from the group consisting of C_{1-15} alkyl, aryl, or heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, monoalkylamino, dialkylamino, alkyl amide, aryl amide, heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3, or heteroaryl; and

R_{23} is selected from the group consisting of H, C_{1-15} alkyl, aryl, or heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, mono- or dialkylamino, alkyl, CN, -O-C_{1-6} alkyl, or CF_3.

In another embodiment, this invention is a compound having the formula above wherein X = -O- or $(CH_2)_n$; Y = -OH or hydrogen; n = 0 or 1; m = 0 or 1;

R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halo, CF_3, OR^{22} and C_{1-4} alkyl wherein R^{22} is a member selected from the group consisting of C_{1-3} alkyl;

R^6, R^7 and R^8 each independently selected from the group consisting of hydrogen and C_{1-3} alkyl;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from hydrogen, C_{1-4} alkyl, or R^9 and R^{10} may together form a carbonyl, or R^{15} and R^{16} may together form a carbonyl or R^{10} and R^{11} may together form $-CH_2CH_2CH_2CH_2-$; and

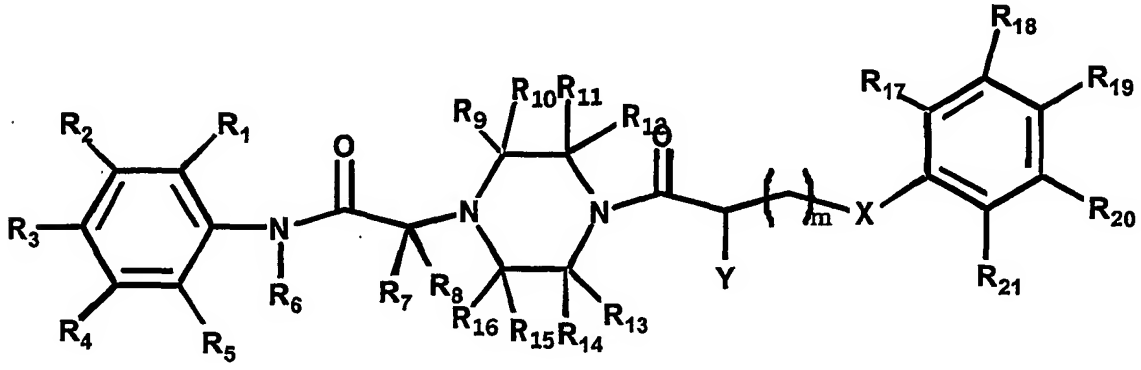
R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR^{22}, $S(O)R^{22}$, SO_2R^{22}, $SON(R^{22})_2$, $CON(R^{22})_2$, C_{1-4} alkyl, or R^{17} and R^{18} may together form -CH=CH-CH=CH-, or R^{18} and R^{19} may together form $-OCH_2O-$, wherein R^{22} is C_{1-3} alkyl.

In still another embodiment, this invention is a substituted piperazine compound selected from the group consisting of N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-3-phenylpropanoyl)piperazinyl]acetamide, N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-3-indol-3-ylpropanoyl)piperazinyl]acetamide, N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-4-phenylbutanoyl)piperazinyl]acetamide, N-(2,6-dimethylphenyl)-2-{4-[2-(2-chlorophenoxy)acetyl]piperazinyl}acetamide, N-(2,6-dimethylphenyl)-2-[4-(4-phenylbutanoyl)piperazinyl]acetamide, N-(2,6-dimethylphenyl)-2-[4-(3-phenylpropanoyl)piperazinyl]acetamide, N-(2,6-dimethylphenyl)-2-[4-(2-phenylacetyl)piperazinyl]acetamide, N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-3-indol-3-ylpropanoyl)piperazinyl]acetamide, and 2-[4-((2R)-2-hydroxy-4-phenylbutanoyl)piperazinyl]-N-(2,6-dimethylphenyl)acetamide.

In yet another embodiment, this invention is a method for administering one or more composition of this invention to a mammal in a treatment selected from the group consisting of protecting skeletal muscles against damage resulting from trauma, protecting skeletal muscles subsequent to muscle or systemic diseases such as intermittent claudication, to treat shock conditions, to preserve donor tissue and organs used in transplants, and to treat cardiovascular diseases including atrial and ventricular arrhythmias, Prinzmetal's (variant) angina, stable angina, and exercise induced angina, congestive heart disease, and myocardial infarction.

DETAILED DESCRIPTION OF THE INVENTION

This invention concerns substituted piperazine compounds having the following formula:



I

wherein X = -O- or $(CH_2)_n$;

Y = -OH or hydrogen;

n = 0 or 1;

m = 0 or 1;

R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halo, CF_3, OR^{22} and C_{1-4} alkyl wherein R^{22} is a member selected from the group consisting of C_{1-3} alkyl;

R^6, R^7 and R^8 each independently selected from the group consisting of hydrogen and C_{1-3} alkyl;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from hydrogen, C_{1-4} alkyl, or R^9 and R^{10} may together form a carbonyl, or R^{15} and R^{16} may together form a carbonyl or R^{10} and R^{11} may together form $-CH_2CH_2CH_2CH_2-$; and

R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR^{22}, $S(O)R^{22}$, SO_2R^{22}, $SON(R^{22})_2$, $CON(R^{22})_2$, C_{1-4} alkyl, or R^{17} and R^{18} may together form -CH=CH-CH=CH-, or R^{18} and R^{19} may together form $-OCH_2O-$, wherein R^{22} is C_{1-3} alkyl.

In preferred compositions, R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, OR^{22} and C_{1-4} alkyl wherein R^{22} is a member selected from the group consisting of C_{1-3} alkyl;

R^6, R^7 and R^8 each independently selected from the group consisting of hydrogen and methyl;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from hydrogen, and C_{1-3} alkyl; and

R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, OR^{22}, C_{1-2} alkyl, or R^{18} and R^{19} may together form $-OCH_2O-$, wherein R^{22} is C_{1-2} alkyl.

In still more preferred compositions, R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, and C_{1-2} alkyl;

R^6, R^7 and R^8 are each hydrogen;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from hydrogen, ethyl and methyl; and

R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, OR^{22}, methyl, wherein R^{22} is methyl.

In yet more preferred compositions, R^1 and R^5 are each methyl;

R^2, R^3, R^4, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each hydrogen; and

R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen and halo.

Most preferably, the substituted piperazine compounds of this invention are selected from the group consisting of N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-3-phenylpropanoyl)piperazinyl]acetamide, N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-3-indol-3-ylpropanoyl)piperazinyl]acetamide, N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-4-phenylbutanoyl)piperazinyl]acetamide, N-(2,6-dimethylphenyl)-2-{4-[2-(2-chlorophenoxy)acetyl]piperazinyl}acetamide, N-(2,6-dimethylphenyl)-2-[4-(4-phenylbutanoyl)piperazinyl]acetamide, N-(2,6-dimethylphenyl)-2-[4-(3-phenylpropanoyl)piperazinyl]acetamide, N-(2,6-dimethylphenyl)-2-[4-(2-phenylacetyl)piperazinyl]acetamide, N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-3-indol-3-ylpropanoyl)piperazinyl]acetamide, and 2-[4-((2R)-2-hydroxy-4-phenylbutanoyl)piperazinyl]-N-(2,6-dimethylphenyl)acetamide.

The following definitions apply to terms as used herein.

"Halo" or "Halogen" - alone or in combination means all halogens, that is, chloro (Cl), fluoro (F), bromo (Br), iodo (I).

"Hydroxyl" refers to the group -OH.

"Thiol" or "mercapto" refers to the group -SH.

"Alkyl" - alone or in combination means an alkane-derived radical containing from 1 to 20, preferably 1 to 15, carbon atoms (unless specifically defined). It is a straight chain

alkyl, branched alkyl or cycloalkyl. Preferably, straight or branched alkyl groups containing from 1-15, more preferably 1 to 8, even more preferably 1-6, yet more preferably 1-4 and most preferably 1-2, carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl and the like. The term "lower alkyl" is used herein to describe the straight chain alkyl groups described immediately above. Preferably, cycloalkyl groups are monocyclic, bicyclic or tricyclic ring systems of 3-8, more preferably 3-6, ring members per ring, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl and the like. Alkyl also includes a straight chain or branched alkyl group that contains or is interrupted by a cycloalkyl portion. The straight chain or branched alkyl group is attached at any available point to produce a stable compound. Examples of this include, but are not limited to, 4-(isopropyl)-cyclohexylethyl or 2-methyl-cyclopropylpentyl. A substituted alkyl is a straight chain alkyl, branched alkyl, or cycloalkyl group defined previously, independently substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, or the like.

"Alkenyl" - alone or in combination means a straight, branched, or cyclic hydrocarbon containing 2-20, preferably 2-17, more preferably 2-10, even more preferably 2-8, most preferably 2 to 4 carbon atoms with at least one, preferably 1-3, more preferably 1-2, and most preferably one, carbon to carbon double bond. In the case of a cycloalkyl group, conjugation of more than one carbon to carbon double bond is not such as to confer aromaticity to the ring. Carbon to carbon double bonds may be either contained within a cycloalkyl portion, with the exception of cyclopropyl, or within a straight chain or branched portion. Examples of alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, cyclohexenyl, cyclohexenylalkyl and the like. A substituted alkenyl is the straight chain alkenyl, branched alkenyl or cycloalkenyl group defined previously, independently substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, carboxy, alkoxycarbonyl, aryloxycarbonyl,

heteroaryloxycarbonyl, or the like attached at any available point to produce a stable compound.

"Alkynyl" - alone or in combination means a straight or branched hydrocarbon containing 2-20, preferably 2-17, more preferably 2-10, even more preferably 2-8, most preferably 2-4, carbon atoms containing at least one, preferably one, carbon to carbon triple bond. Examples of alkynyl groups include ethynyl, propynyl, butynyl and the like. A substituted alkynyl refers to the straight chain alkynyl or branched alkynyl defined previously, independently substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, or the like attached at any available point to produce a stable compound.

"Alkyl alkenyl" refers to a group -R-CR'=CR''' R'''', where R is lower alkyl, or substituted lower alkyl, R', R''', R'''' may independently be hydrogen, halogen, lower alkyl, substituted lower alkyl, acyl, aryl, substituted aryl, hetaryl, or substituted hetaryl as defined below.

"Alkyl alkynyl" refers to a groups -RC≡CR' where R is lower alkyl or substituted lower alkyl, R' is hydrogen, lower alkyl, substituted lower alkyl, acyl, aryl, substituted aryl, hetaryl, or substituted hetaryl as defined below.

"Alkoxy" denotes the group -OR, where R is lower alkyl, substituted lower alkyl, acyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heteroalkyl, heteroarylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, or substituted cycloheteroalkyl as defined.

"Alkylthio" denotes the group -SR, $-S(O)_{n=1-2}-R$, where R is lower alkyl, substituted lower alkyl, aryl, substituted aryl, aralkyl or substituted aralkyl as defined herein.

"Acyl" denotes groups -C(O)R, where R is hydrogen, lower alkyl substituted lower alkyl, aryl, substituted aryl and the like as defined herein.

"Aryloxy" denotes groups -OAr, where Ar is an aryl, substituted aryl, heteroaryl, or substituted heteroaryl group as defined herein.

"Amino" denotes the group NRR', where R and R' may independently by hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, hetaryl, or substituted hetaryl as

defined herein or acyl.

"Amido" denotes the group -C(O)NRR', where R and R' may independently by hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, hetaryl, substituted hetaryl as defined herein.

"Carboxyl" denotes the group -C(O)OR, where R is hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, hetaryl, and substituted hetaryl as defined herein.

"Aryl" - alone or in combination means phenyl or naphthyl optionally carbocyclic fused with a cycloalkyl of preferably 5-7, more preferably 5-6, ring members and/or optionally substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, or the like.

"Substituted aryl" refers to aryl optionally substituted with one or more functional groups, *e.g.*, halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Heterocycle" refers to a saturated, unsaturated, or aromatic carbocyclic group having a single ring (*e.g.*, morpholino, pyridyl or furyl) or multiple condensed rings (*e.g.*, naphthpyridyl, quinoxalyl, quinolinyl, indolizinyl or benzo[b]thienyl) and having at least one hetero atom, such as N, O or S, within the ring, which can optionally be unsubstituted or substituted with, *e.g.*, halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Heteroaryl" - alone or in combination means a monocyclic aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing one or more, preferably 1-4, more preferably 1-3, even more preferably 1-2, heteroatoms independently selected from the group O, S, and N, and optionally substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl

or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, or the like. Heteroaryl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. A carbon or nitrogen atom is the point of attachment of the heteroaryl ring structure such that a stable aromatic ring is retained. Examples of heteroaryl groups are pyridinyl, pyridazinyl, pyrazinyl, quinazolinyl, purinyl, quinolinyl, isoquinolinyl, pyrimidinyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, oxathiadiazolyl, isothiazolyl, tetrazolyl, imidazolyl, triazinyl, furanyl, benzofuryl, indolyl, benzothiazolyl, benzoxazolyl, and the like. A substituted heteroaryl contains a substituent attached at an available carbon or nitrogen to produce a stable compound.

"Heterocyclyl" - alone or in combination means a non-aromatic cycloalkyl group having from 5 to 10 atoms in which from 1 to 3 carbon atoms in the ring are replaced by heteroatoms of O, S or N, and are optionally benzo fused or fused heteroaryl of 5-6 ring members and/or are optionally substituted as in the case of cycloalkyl. Heterocycyl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. The point of attachment is at a carbon or nitrogen atom. Examples of heterocyclyl groups are tetrahydrofuranyl, dihydropyridinyl, piperidinyl, pyrrolidinyl, piperazinyl, dihydrobenzofuryl, dihydroindolyl, and the like. A substituted hetercyclyl contains a substituent nitrogen attached at an available carbon or nitrogen to produce a stable compound.

"Substituted heteroaryl" refers to a heterocycle optionally mono or poly substituted with one or more functional groups, *e.g.*, halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Aralkyl" refers to the group -R-Ar where Ar is an aryl group and R is lower alkyl or substituted lower alkyl group. Aryl groups can optionally be unsubstituted or substituted with, *e.g.*, halogen, lower alkyl, alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Heteroarylalkyl" refers to the group -R-HetAr where HetAr is an heteroaryl group and R lower alkyl or substituted lower alkyl. Heteroarylalkyl groups can optionally be unsubstituted or substituted with, *e.g.*, halogen, lower alkyl, substituted lower alkyl, alkoxy, alkylthio, acetylene, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Cycloalkyl" refers to a divalent cyclic or polycyclic alkyl group containing 3 to 15

carbon atoms.

"Substituted cycloalkyl" refers to a cycloalkyl group comprising one or more substituents with, *e.g.*, halogen, lower alkyl, substituted lower alkyl, alkoxy, alkylthio, acetylene, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Alkyl cycloalkyl" denotes the group -R-cycloalkyl where cycloalkyl is a cycloalkyl group and R is a lower alkyl or substituted lower alkyl. Cycloalkyl groups can optionally be unsubstituted or substituted with *e.g.* halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Optional" and "optionally" mean that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optional pharmaceutical excipients" indicates that a formulation so described may or may not include pharmaceutical excipients other than those specifically stated to be present, and that the formulation so described includes instances in which the optional excipients are present and instances in which they are not.

"Treating" and "treatment" refer to any treatment of a disease in a mammal, particularly a human, and include:

(i) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it;

(ii) inhibiting the disease, i.e., arresting its development; or

(iii) relieving the disease, i.e., causing regression of the disease.

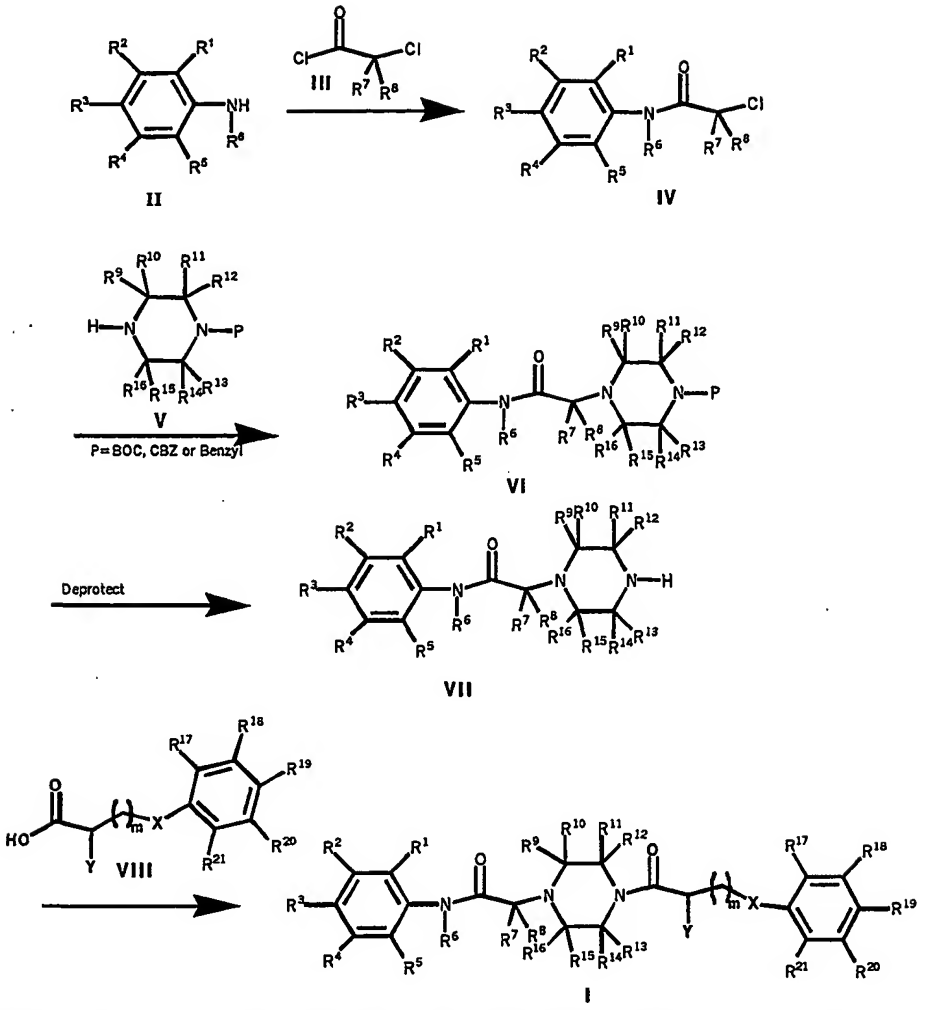
The compositions of this invention are useful for treating mammals in a therapy selected from the group consisting of protecting skeletal muscles against damage resulting from trauma, protecting skeletal muscles subsequent to muscle or systemic diseases such as intermittent claudication, to treat shock conditions, to preserve donor tissue and organs used in transplants, and to treat cardiovascular diseases including atrial and ventricular arrhythmias, Prinzmetal's (variant) angina, stable angina, and exercise induced angina, congestive heart disease, and myocardial infarction. The treatment is accomplished using a therapeutically effective amount of at least one compound of this invention and/or a pharmaceutically acceptable acid addition salt thereof in admixture with a pharmaceutically acceptable excipient.

Compounds falling within the scope of this invention include the optical isomers (+) and (-) and R- and S- isomers of the above-identified compounds and mixtures thereof. This invention includes the individual isomers and all possible mixtures thereof.

All of the aforementioned embodiments include the pharmaceutically acceptable acid addition salts thereof, particularly the mono- and dihydrochlorides, and mixtures thereof.

The compounds having the general formula **I** can be prepared as outlined in Schemes 1-5. A general synthesis of the compounds of this invention is outlined in Scheme 1. Compound **IV** can be prepared by N-acylation of substituted aniline **II** with 2-substituted chloroacetylchloride **III**. Compound **II** is available commercially or readily prepared through reduction of the corresponding nitrobenzene derivative (acid/$SnCl_2$ or catalytic hydrogenation, see Advanced Organic Chemistry, Ed. J. March, (1992) A. Wiley-Interscience). Some examples of commercially available substituted aniline **II** include 2,6-dimethylaniline, 2,3-dimethylaniline, 2-methylaniline 4-methylaniline, 4-methylaniline, 2,4-dichloroaniline, 3,4-dichloroaniline, 2,5-dichloroaniline, 2,4-dichloroaniline, 2-chloroaniline, 3-chloroaniline, 2,6-difluoroaniline, 2,5-difluoroaniline, 3,4-difluoroaniline, 2-fluoroaniline, 4-fluoroaniline, 3-fluoroaniline, 2-fluoro-6-chloroaniline, 4-fluoro-3-chloroaniline.

SCHEME 1

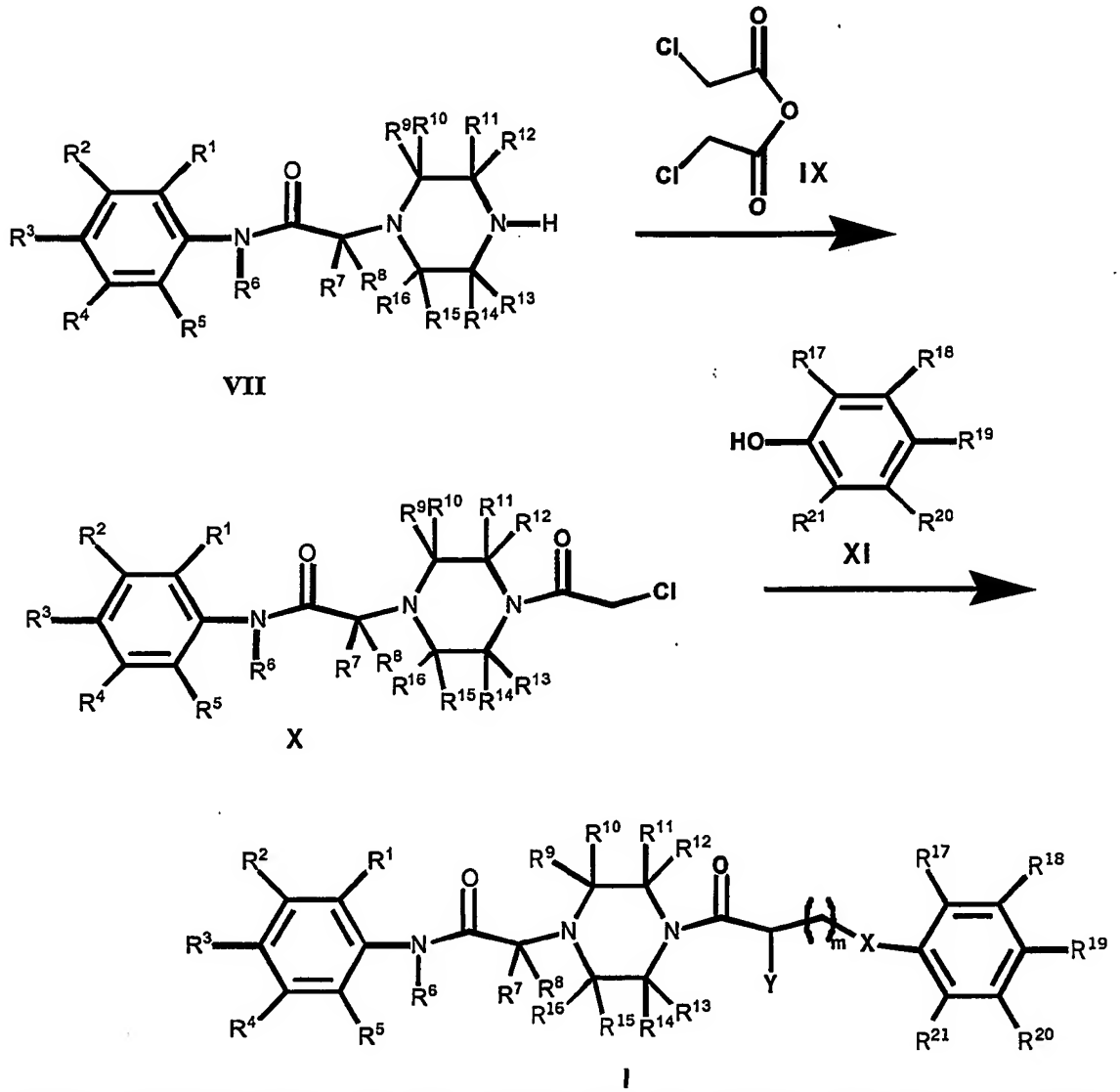


Compound **VI** can be obtained by reacting compound **IV** with N-protected substituted piperazine **V** through warming in an appropriate solvent (e.g. DMF, EtOH). Protection of the nitrogen of compound **V** is only required when it is useful to control the regiochemistry of the addition of Compound **V** with compound **IV**. In some cases, compound **V** can be obtained from commercial sources. Examples of commercially available compounds of general structure **V** include 2-methyl piperazine, 2,5-dimethyl piperazine, 2,6-dimethyl piperazine and 4-benzyloxycarbonylpiperazin-2-one. Deprotection of compound **VI** can be accomplished using the standard conditions (e.g. for Boc group use TFA, for CBZ and benzyl use hydrogenation). Compound **I** can be prepared by coupling compound **VII** with carboxylic acid **VIII** (eg. EDC or HBTU). Compound **VIII** can be obtained from commercial sources. Examples of commercially available compounds corresponding to general structure **VIII** include -phenyllactic acid, 3-Indollactic acid, R-2-hydroxy-4-phenylbutyric acid, hydrocinnamic acid, 3-(2-methoxyphenyl)propionic acid, 3-

(2,3,4-trimethoxyphenyl)propionic acid, 3-(2,3,-dimethoxyphenyl)propionic acid, and 4-phenylbutyric acid.

Compound I can alternatively be prepared as described in scheme 2. Compound X can be obtained through N-acylation of VII with chloroacetic anhydride.

SCHEME 2

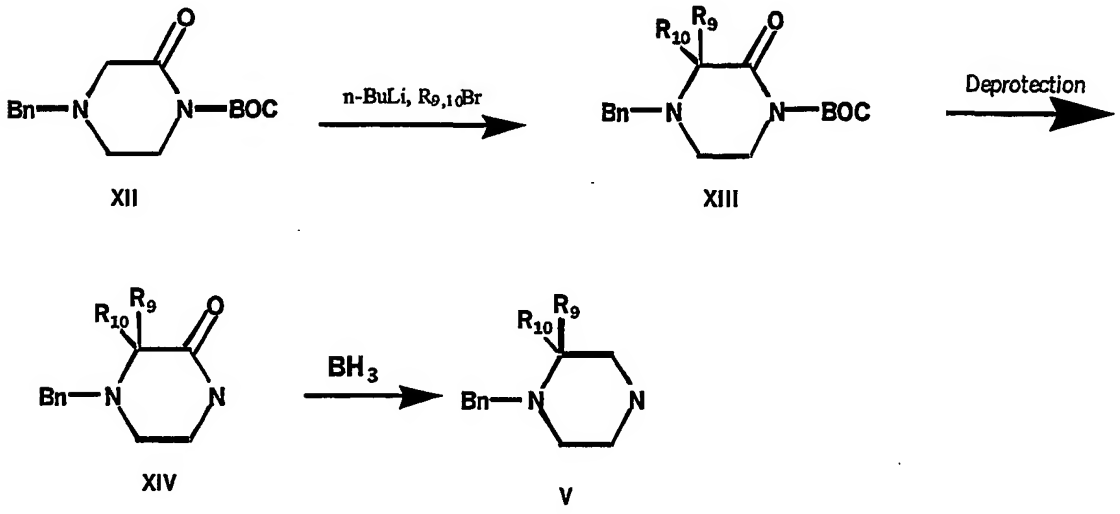


Heating substituted phenol XI with compound X with potassium carbonate in acetone yields compound I wherein Y=H, m=0, X=O. Examples of commercially available substituted phenols include 2-chlorophenol, 2-fluorophenol, 2-methoxyphenol, 2-methylphenol, sesamol, 2,6-dichlorophenol, 3,5-dichlorophenol, 2,6-difluorophenol, 2,4-difluorophenol, 5-indanol, 3-chloro-4-fluorophenol, 2-chloro-4-fluorophenol and 5,6,7,8-tetrahydro-2-naphthol.

Compound V can be prepared as described in Scheme 3. Alkylation of compound XII with alkyl halides using t-BuLi as base can afford compound XIII as described by Pohlman et. al. (J. Org. Chem, (1997), 62, 1016-1022). Reduction of XIV using diborane can afford

N-benzyl protected version of compound V after N-Boc deprotection with trifluoroacetic acid (TFA , for the diborane reduction see Jacobson et. al, J. Med. Chem, (1999), 42, 1123-1144).

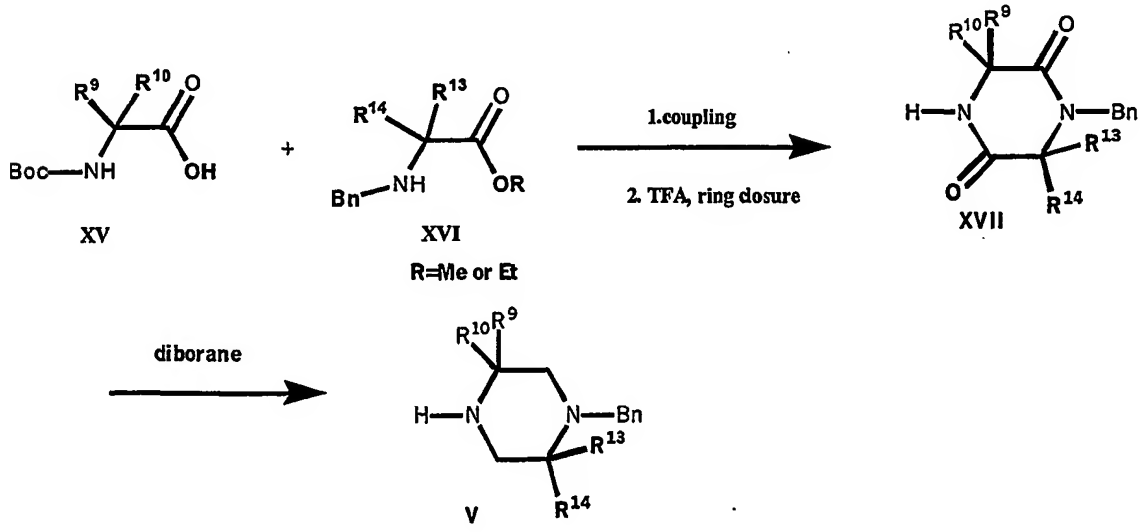
SCHEME 3



XII XIII XIV V

Compound V can also be prepared through standard coupling (eg. EDC or PyBroP) and deprotection of D or L amino acids as outlined in Scheme 4 [For preparations of diketopiperazines see – P. Cledera et al. Tetrahedron, (1998) p. 12349-12360 and R. A. Smith et al Bioorg. Med. Chem. Lett. (1998) p. 2369-2374]. Reduction of the diketopiperazine with diborane can afford the N-benzyl protected version of compound V.

SCHEME 4

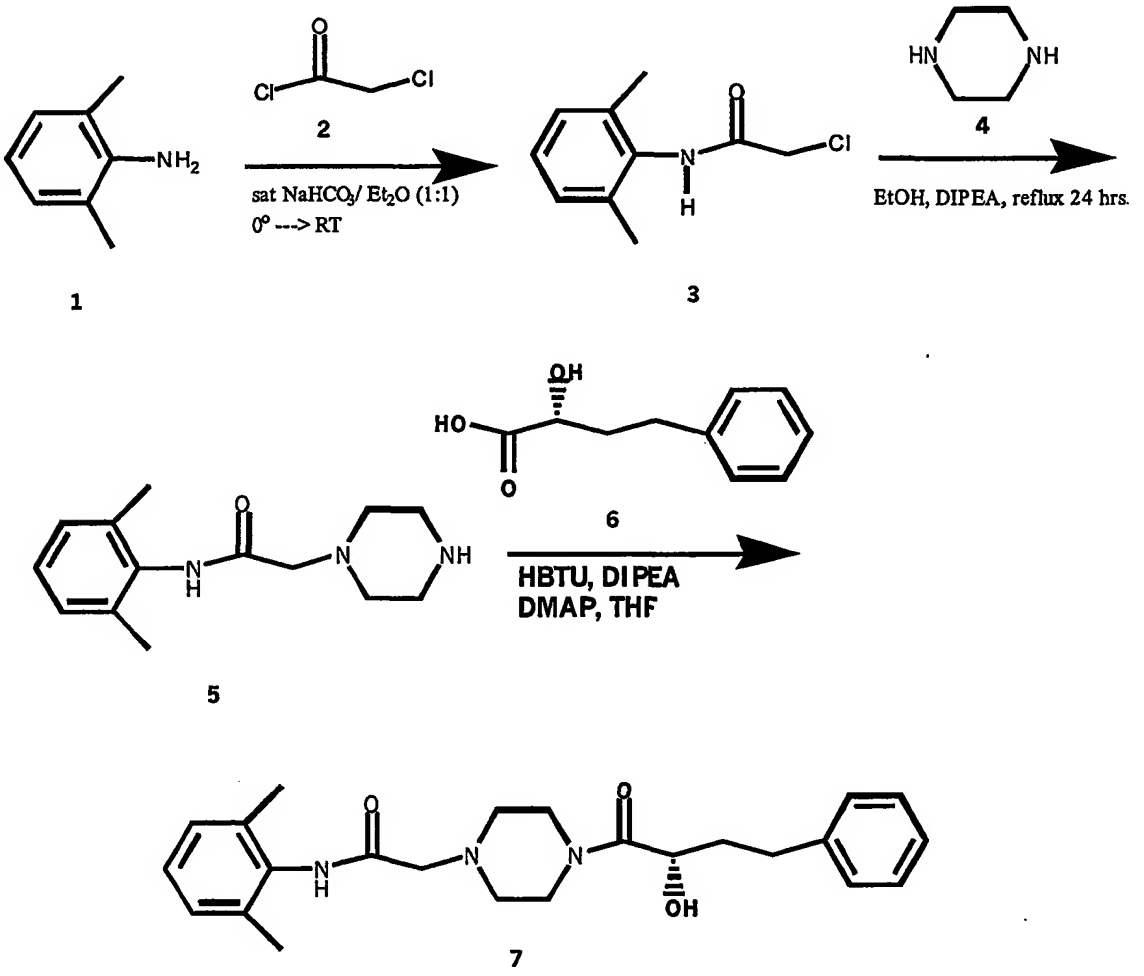


XV XVI XVII V

R=Me or Et

A specific example of the preparation of a compound from this invention is disclosed in Scheme 5 to further illustrate how to prepare the compounds of this invention. In particular, 2,6-dichloroaniline **1** was acylated with 2-chloroacetyl chloride **2** using saturated bicarbonate and ether (1:1) as base and co-solvent, respectively to afford the chloroacetamide derivative **3**. Further reaction of compound **3** with piperazine afforded compound **5** through warming in ethanol. Coupling of compound **5** with (R)-2-hydroxy-phenylbutyric acid using standard amino acid coupling conditions (HBTU, DIPEA,DMAP and THF) yields compound **7**.

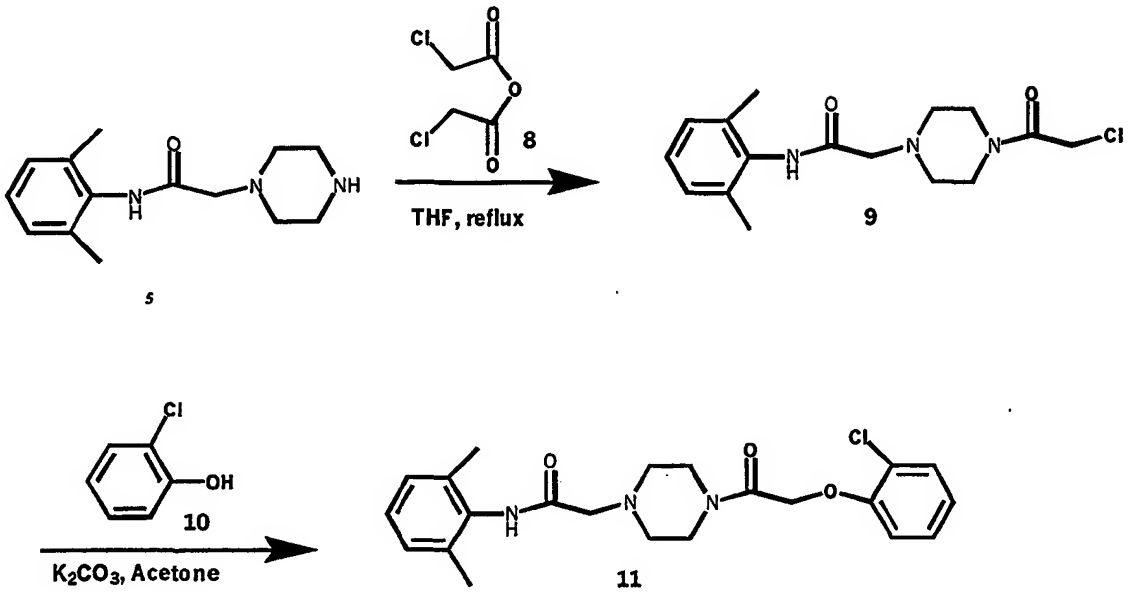
SCHEME 5



A second example of the preparation of a compound from this invention is disclosed in Scheme 6 to further illustrate how to prepare the compounds of this invention. In particular, previously synthesized **5** was acylated with chloroacetic anhydride **8** to yield the substituted

piperazine derivative **9**. Compound **11** is prepared by heating compound **9** with 2-chlorophenol in ethanol with potassium carbonate.

SCHEME 6



The acid addition salts of the compounds of this invention may be converted to the corresponding free base by treating with a suitable base, such as potassium carbonate or sodium hydroxide, typically in the presence of aqueous solvent, and at a temperature of between about 0 degrees C and 100 degrees C. The free base form is isolated by conventional means, such as extraction with an organic solvent.

Salts of the compounds of this invention may be interchanged by taking advantage of differential solubilities and volatilities, or by treating with the appropriately loaded ion exchange resin. This conversion is carried out at a temperature between about 0°C and the boiling point of the solvent being used as the medium for the procedure. Administration of the active compounds and salts described herein can be via any of the accepted modes of administration for therapeutic agents. These methods include oral, parenteral, transdermal, subcutaneous and other systemic modes. The preferred method of administration is oral, except in those cases where the subject is unable to ingest, by himself, any medication. In those instances it may be necessary to administer the composition parentarally.

Depending on the intended mode, the compositions may be in the form of solid, semi-solid or liquid dosage forms, such as, for example, tablets, suppositories, pills, capsules, powders, liquids, suspensions, or the like, preferably in unit dosage forms suitable for single

administration of precise dosages. The compositions may include one or more conventional pharmaceutical excipients and at least one active compound of this invention or the pharmaceutically acceptable salts thereof and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, diluents, etc.

The amount of active compound administered will, of course, be dependent on the subject being treated, the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician. However, an effective dosage is in the range of 0.1-30 mg/kg/day, preferably 0.5-20 mg/kg/day. For an average 70 kg human, this would amount to 7-2100 mg per day, or preferably 35-1400 mg/day. Since many of the effects of the compounds herein (protect skeletal muscles against damage resulting from trauma; protect skeletal muscles subsequent to muscle or systemic diseases such as intermittent claudication; treat shock conditions; preserve donor tissue and organs used in transplants; and treat cardiovascular diseases including atrial and ventricular arrhythmias, Prinzmetal's (variant) angina, stable angina, exercise induced angina, congestive heart disease, and myocardial infarction) are achieved through a similar mechanism (partial fatty acid oxidation inhibition) dosages (and forms of administration) are all generally within the same general and preferred ranges for all these utilities.

For solid compositions, conventional non-toxic solid include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like may be used. The active compound as defined above may be formulated as suppositories using, for example, polyalkylene glycols, for example, propylene glycol, as the carrier. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc. an active compound as defined above and optional pharmaceutical adjuvants in a excipient, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 15th Edition, 1975. The composition or formulation to be administered will, in any event, contain a quantity of the active compound(s), a therapeutically effective amount, i.e. in an amount effective to alleviate the symptoms of the subject being treated. For oral

administration, a pharmaceutically acceptable non-toxic composition is formed by the incorporation of any of the normally employed excipients, such as, for example pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium, carbonate, and the like. Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations and the like. Such compositions may contain 10%-95% active ingredient, preferably 1-70%.

Parenteral administration is generally characterized by injection, either subcutaneously, intramuscularly or intravenously. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol or the like. In addition, if desired, the pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, etc.

A more recently devised approach for parenteral administration employs the implantation of a slow-release or sustained-release system, such that a constant level of dosage is maintained. See, e.g., U.S. Pat. No. 3,710,795, which is incorporated herein by reference. In another recent approach, the compositions of this invention can be administered orally in a sustained release dosage form using the compositions and/or methods disclosed in U.S. Patent Application Serial No. 09/321,522, filed on May 27, 1999, the specification of which is incorporated herein by reference.

It is within the scope of this invention to administer one or more compounds of this invention to a mammal, and preferably to a human by other known routes of pharmaceutical dosage form administration including, but not limited to by bolus, intravenously, transdermally, through inhalation, sub-cutaneously, or any other therapeutic agent administration method or route know to one skilled in the art.

The following Examples are representative of the invention, but are not to be construed as limiting the scope of the claims.

Example 1

N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-4-phenylbutanoyl)piperazinyl]acetamide

Part A: Synthesis of N-(2,6-dimethylphenyl)-2-chloroacetamide (3).

2,6-dimethylaniline (9.8 g, 81.2 mmol) was dissolved in ether (100 mL) and saturated aqueous $NaHCO_3$ (100 mL) and the reaction mixture was cooled in an ice/water bath. To the cold solution was added chloroacetyl chloride **2** (9.17 g, 81.2 mmol) dropwise over a period of 2 h. The mixture was allowed to warm to RT over 14 h. The mixture was diluted with 100 mL ether and the organic layer was dried over $MgSO_4$, filtered and concentrated to afford compound **3** as a white solid.

Part B.

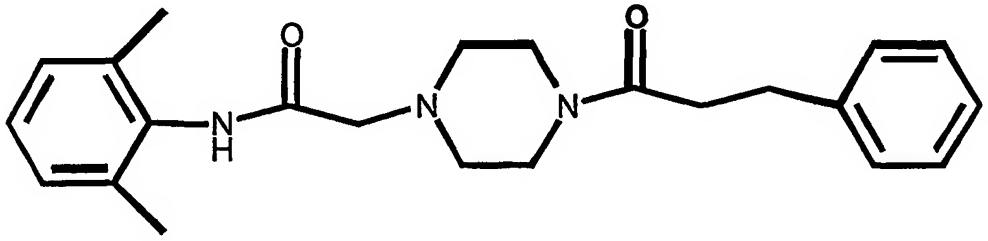
Synthesis of N-(2,6-dimethylphenyl)-2-piperazinylacetamide (5).

To a solution of compound **3** in 100 mL EtOH (5 g, 25.2 mmol) was added compound **4** (2.1 g, 25.0 mmol) and N,N-diisopropylethylamine (3.2 g, 25.2 mmol). The reaction mixture was refluxed for 24 h. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (10:1, DCM:MeOH) to afford compound **5**..

Part C.

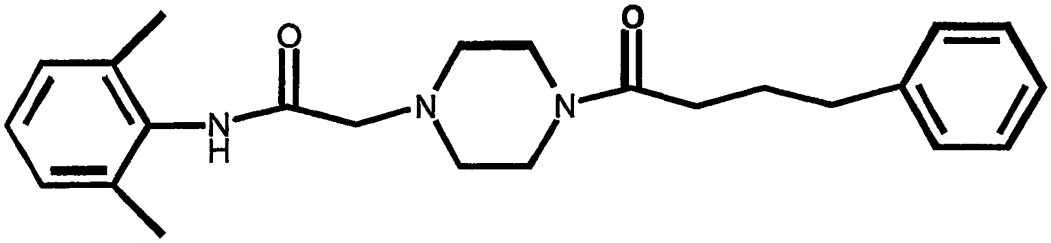
Synthesis of N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-4phenylbutanoyl) piperazinyl]acetamide (7)

To a solution of **5** in 10ml DMF (0.263g, 1.07mmol) was added compound **6** (0.25g, 1.39mmol), HBTU (0.526g, 1.4mmol), triethylamine (0.108g, 1.07mmol) and DMAP (0.030g, 0.25mmol). The solution was allowed to stir at room temperature for 48h. The solution was concentrated *in vacuo*. The residue was taken into EtOAc (100ml) and washed with saturated sodium bicarbonate (3x50ml). The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The residue was purified using prep. TLC (10:1 DCM/MeOH) to afford compound **7**: Mass spectrum (M+1) = 410.44.



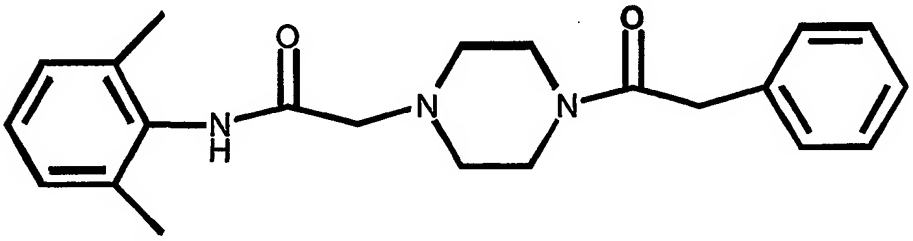
N-(2,6-dimethylphenyl)-2-[4-(3-phenylpropanoyl)piperazinyl]acetamide (12)

Compound **12** was prepared in the manner of compound **7** substituting 3-phenylpropanoic acid for (R)-2-hydroxy-phenylbutyric acid in part C to afford compound **12**: Mass spectrum (M+1) = 380.40.



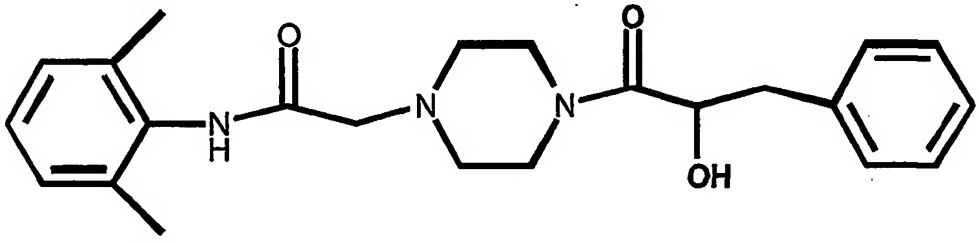
N-(2,6-dimethylphenyl)-2-[4-(4-phenylbutanoyl)piperazinyl]acetamide (13)

Compound **13** was prepared in the manner of compound **7** substituting 4-phenylbutanoic acid for (R)-2-hydroxy-phenylbutyric acid in part C to afford compound **13**: Mass spectrum (M+1) = 394.40.



N-(2,6-dimethylphenyl)-2-[4-(2-phenylacetyl)piperazinyl]acetamide (14)

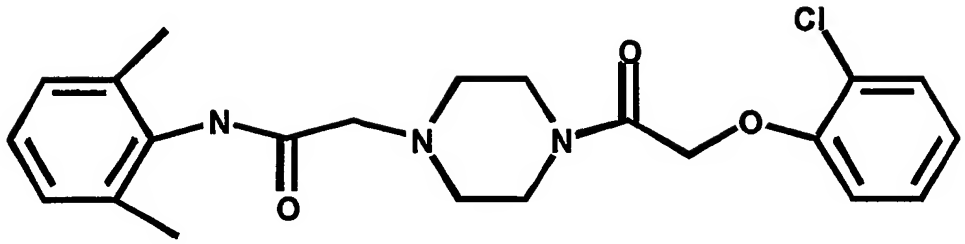
Compound **14** was prepared in the manner of compound **7** substituting 2-phenylacetic acid for (R)-2 hydroxy-phenylbutyric acid in part C to afford compound **14**: Mass spectrum (M+1) = 366.40.



N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-3-phenylpropanoyl)piperazinyl]acetamide (15)

Compound **15** was prepared in the manner of compound **7** substituting 2-hydroxy-3-phenylpropanoic acid for (R)-2-hydroxy-phenylbutyric acid in part C to afford compound **15**: Mass spectrum (M+1) = 396.35.

Example 2



11

N-(2,6-dimethylphenyl)-2-{4-[2-(2-chlorophenoxy)acetyl]piperazinyl}acetamide (11)

Part A.

Synthesis of N-(2,6-dimethylphenyl)-2-chloroacetamide (3).

2,6-dimethylaniline (9.8 g, 81.2 mmol) was dissolved in ether (100 mL) and saturated aqueous $NaHCO_3$ (100 mL) and the reaction mixture was cooled in an ice/water bath. To the cold solution was added chloroacetyl chloride **2** (9.17 g, 81.2 mmol) dropwise over a period of 2 h. The mixture was allowed to warm to RT over 14 h. The mixture was diluted with 100 mL ether and the organic layer was dried over $MgSO_4$, filtered and concentrated to afford compound **3** as a white solid.

Part B.

Synthesis of N-(2,6-dimethylphenyl)-2-piperazinylacetamide (5).

To a solution of compound **3** in 100 mL EtOH (5 g, 25.2 mmol) was added compound **4** (2.1 g, 25.0 mmol) and N,N-diisopropylethylamine (3.2 g, 25.2 mmol). The reaction mixture was refluxed for 24 h. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (10:1, DCM:MeOH) to afford compound **5**..

Part C.

Synthesis of N-(2,6-dimethylphenyl)-2-[4-(2-chloroacetyl)piperazinyl]acetamide (9)

To a solution of **5** (1g, 4mmol) in 15ml THF was added chloroacetic anhydride (0.692g, 4mmol). The solution was heated to reflux for one hour. The solvent was evaporated *in vacuo* and the residue was purified using flash chromatography to yield compound **9**.

Part D.

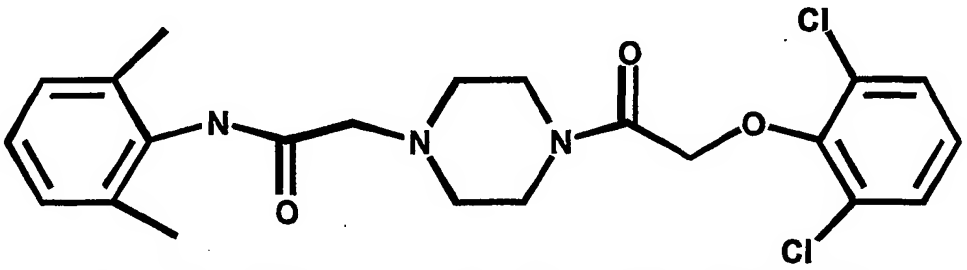
Synthesis of N-(2,6-dimethylphenyl)-2-{4-[2-(2 chlorophenoxy)acetyl]piperazinyl}acetamide (11)

To a solution of **9** (0.194g, 0.6mmol) in 4ml acetone was added 2-chlorophenol (0.092g, 0.72mmol) and potassium carbonate (0.3g, 2.2mmol). The solution was heated to reflux and stirred for 48h. The solution was filtered to remove potassium carbonate, concentrated *en*

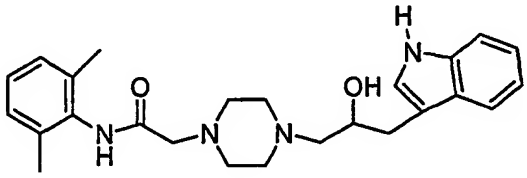
vacuo, and purified by Prep TLC (10:1 DCM:MeOH) to yield compound **11**. Mass spectrum (M+1) = 416.32

2-{4-[2-(2,6-dichlorophenoxy)acetyl]piperazinyl}-N-(2,6-dimethylphenyl)acetamide (16)

Compound **16** was prepared in a similar manner to **11** substituting 2,6-dichlorophenol with 2-

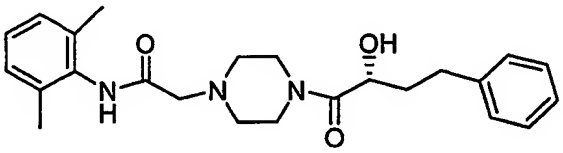


chlorophenol in part D to afford compound **16**. Mass spectrum (M+1) =451.23



N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-3-indol-3-ylporpanoyl)piperazinyl]acetamide (17)

Compound **17** was prepared in the manner of compound 7 substituting indole-3-lactic acid for (R)-2-hydroxy-phenylbutyric acid in part C to afford compound **17**. Mass spectrum (M + 1) = 435.46.



2-[4-((2R)-2-hydroxy-4-phenylbutanoyl)piperazinyl]-N-(2,6-dimethylphenyl)acetamide (18)

Compound **18** was prepared in the manner of compound 7 substituting R-2-hydroxy-4-phenylbutyric acid for (R)-2-hydroxy-phenylbutyric acid in part C to afford compound **18**. Mass spectrum (M + 1) = 410.44.

Example 3

Mitochondrial Assays

Rat heart mitochodria were isolated by the method of Nedergard and Cannon (Methods in Enzymol. 55, 3, 1979).

Palmitoyl CoA oxidation – The Palmitoyl CoA oxidation was carried out in a total volume of 100 microliters containing the following agents: 110 mM KCl, 33 mM Tris buffer at pH 8, 2 mM KPi, 2 mM $MgCl_2$, 0.1 mM EDTA, 14.7 microM defatted BSA, 0.5 mM malic acid, 13 mM carnitine, 1 mM ADP, 52 micrograms of mitochondrial protein, and 16 microM 1-C14 palmitoyl CoA (Sp. Activity 60 mCi/mmole; 20 microCi/ml, using 5 microliters per assay). The compounds of this invention were added in a DMSO solution at the following concentrations: 100 microM, 30 microM, and 3 microM. In each assay, a DMSO control was used. After 15 min at 30 oC, the enzymatic reaction was centrifuged (20,000 g for 1 min), and 70 microliters of the supernatant was added to an activated reverse phase silicic acid column (approximately 0.5 ml of silicic acid). The column was eluted with 2 ml of water, and 0.5 ml of the eluent was used for scintillation counting to determine the amount of C^{14} trapped as C^{14} bicarbonate ion. The data are presented as % activity of control.

Table 1

Inhibition of mitochondrial fatty acid oxidation using palmitoyl CoA as substrate - % of Control at 3 concentrations.

Compound #	100 μM	30 μM	3 μM
Ranolazine	75%	90%	--
15	64%	--	--
16	65%	--	--
7	78%	--	--
11	80%	--	--
13	82%		
12	78%	96%	103%
17	76%		
18	78%		
14	94%	104%	107%

Example 4

Palmitoyl Carnitine Oxidation – The Palmitoyl carnitine oxidation was carried out in a total volume of 100 microliters containing the following agents: 110 mM KCl, 33 mM Tris buffer at pH 8, 2 mM KPi, 2 mM $MgCl_2$, 0.1 mM EDTA, 0.1 mg/ml of defatted BSA, 0.5 mM malic acid, 3 mM ADP, 52 micrograms of mitochondrial protein, and 43 microM 1-C14 palmitoyl carnitine (Sp. Activity 60 mCi/mmole; 20 microCi/ml, using 5 microliters per assay). The compounds of this invention were added in a DMSO solution at the following concentrations: 100 microM, 30 microM, and 3 microM. In each assay, a DMSO control was used. After 15 min at 30 °C, the enzymatic reaction was centrifuged (20,000 g for 1 min), and 70 microliters of the supernatant was added to an activated reverse phase silicic acid column (approximately 0.5 ml of silicic acid). The column was eluted with 2 ml of water, and 0.5 ml of the eluent was used for scintillation counting to determine the amount of C^{14} trapped as C^{14} bicarbonate ion. The data are presented as % activity of control.

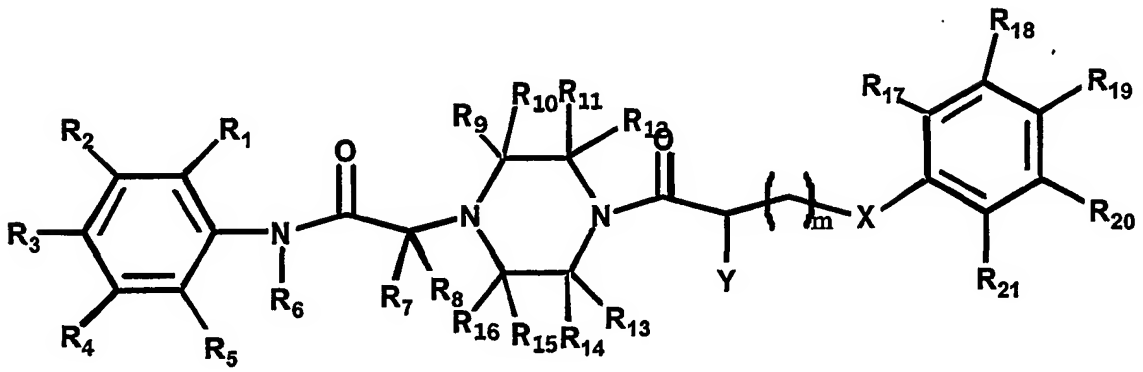
Table 2.

Inhibition of mitochondrial fatty acid oxidation using palmitoyl carnitine as substrate - % of Control at 3 concentrations.

Compound #	100 μM	30 μM	3 μM
Ranolazine	63%	98%	--
15	--	--	--
16	--	--	--
7	--	--	--
11	--	--	--
13	--	--	--
12	79%	98%	103%
14	88	100	103

We claim:

1. A substituted piperazine compound having the following formula:



I

wherein X = -O- or $(CH_2)_n$;

Y = -OH or hydrogen;

n = 0 or 1;

m = 0 or 1;

R_1, R_2, R_3, R_4 and R_5 are each independently selected from the group consisting of hydrogen, halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, SO_2R_{22}, $SO_2N(R_{23})_2$, $NR_{23}CO_2R_{22}$, $NR_{23}CON(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, $NR_{23}SO_2R_{22}$, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl substituent are optionally substituted with 1 substituent selected from the group consisting of halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, and SO_2R_{22};

R_6, R_7 and R_8 each independently selected from the group consisting of hydrogen or C_{1-15} alkyl;

R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of hydrogen, CO_2R_{23}, $CON(R_{23})_2$, C_{1-4} alkyl, or aryl wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, CF_3, CN, OR_{23}, $N(R_{23})_2$, CO_2R_{23}, $CON(R_{23})_2$ or aryl, wherein R_9 and R_{10} may together form a carbonyl, or R_{11} and R_{12} may together form a carbonyl, or R_{13} and R_{14} may together form a carbonyl, or R_{15} and R_{16} may together form a carbonyl wherein R_{11} and R_{13} or R_9 and R_{15} or R_9 and R_{11} or R_{11} and R_{15} or R_9 and R_{13} may join together to form a bridging ring system wherein the two R groups together comprise of from 1 to 4 carbon atoms and wherein R_9 and R_{10} or R_{11} and R_{12} or R_{13} and R_{14} or R_{15} and R_{16} may join to form a bridging ring system wherein the two R groups together comprise of from 1 to 5 carbon atoms;

R_{17}, R_{18}, R_{19}, R_{20}, and R_{21} are each independently selected from the group consisting of

hydrogen, halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, SO_2R_{22}, $SO_2N(R_{23})_2$, $NR_{23}CO_2R_{22}$, $NR_{23}CON(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, $NR_{23}SO_2R_{22}$, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl substituent are optionally substituted with 1 substituent selected from the group consisting of halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, and SO_2R_{22};

R_{22} is selected from the group consisting of C_{1-15} alkyl, aryl, or heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, monoalkylamino, dialkylamino, alkyl amide, aryl amide, heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3, or heteroaryl; and

R_{23} is selected from the group consisting of H, C_{1-15} alkyl, aryl, or heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, mono- or dialkylamino, alkyl, CN, -O-C_{1-6} alkyl, or CF_3.

2. The compound of claim 1 wherein R_1, R_2, R_3, R_4 and R_5 are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $SO_2N(R_{23})_2$, CO_2R_{23}, $CON(R_{23})_2$, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl heterocyclyl, aryl, or heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, and $S(O)R_{22}$, and SO_2R_{22};

R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen or C_{1-8} alkyl;

R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of hydrogen, C_{1-4} alkyl, or aryl wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, CF_3, CN, OR_{23}, $N(R_{23})_2$, CO_2R_{23}, $CON(R_{23})_2$ or aryl, wherein R_9 and R_{10} may together form a carbonyl, or R_{11} and R_{12} may together form a carbonyl, or R_{13} and R_{14} may together form a carbonyl, or R_{15} and R_{16} may together form a carbonyl wherein R_{11} and R_{13} or R_9 and R_{15} or R_9 and R_{11} or R_{11} and R_{15} or R_9 and R_{13} may join together to form a ring including from 1 to 4 carbon atoms and wherein R_9 and R_{10} or R_{11} and R_{12} or R_{13} and R_{14} or R_{15} and R_{16} may join to form a ring including from 1 to 5 carbon atoms; and

R_{17}, R_{18}, R_{19}, R_{20}, and R_{21} are each independently selected from the group consisting of hydrogen, halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, SO_2R_{22}, $SO_2N(R_{23})_2$, $NR_{23}CO_2R_{22}$, $NR_{23}CON(R_{23})_2$, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, $NR_{23}SO_2R_{22}$, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl substituent are optionally substituted with 1 substituent selected from the group consisting of

halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, and SO_2R_{22}

3. The compound of claim 1 wherein R_1, R_2, R_3, R_4 and R_5 are each independently selected from the group consisting of hydrogen, halo, CF_3, OR^{20}, C_{1-5} alkyl, C_{2-5} alkenyl, or C_{2-5} alkynyl, wherein the alkyl substituent is optionally substituted with CF_3;

R_6, R_7 and R_8 are each independently selected from the group consisting of hydrogen or C_{1-3} alkyl;

R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of hydrogen, C_{1-4} alkyl, or aryl wherein the alkyl and aryl substituents are R_1, R_2, R_3, R_4 and R_5 alkyl or aryl, wherein R_9 and R_{10} may together form a carbonyl, or R_{11} and R_{12} may together form a carbonyl, or R_{13} and R_{14} may together form a carbonyl, or R_{15} and R_{16} may together form a carbonyl wherein R_{11} and R_{13} or R_9 and R_{15} or R_9 and R_{11} or R_{11} and R_{15} or R_9 and R_{13} may join together to form a ring including from 1 to 4 carbon atoms and wherein R_9 and R_{10} or R_{11} and R_{12} or R_{13} and R_{14} or R_{15} and R_{16} may join to form a ring including from 1 to 5 carbon atoms;

R_{17}, R_{18}, R_{19}, R_{20}, and R_{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR_{23}, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl substituent are optionally substituted with 1 substituent selected from the group consisting of halo, NO_2, CF_3, CN, OR_{23}, SR_{23}, $N(R_{23})_2$, $S(O)R_{22}$, and SO_2R_{22};

R_{22} is selected from the group consisting of C_{1-15} alkyl, aryl, or heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, monoalkylamino, dialkylamino, alkyl amide, aryl amide, heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3, or heteroaryl; and

R_{23} is selected from the group consisting of H, C_{1-8} alkyl, aryl, or heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, -O-C_{1-3} alkyl, or CF_3.

4. The composition of claim 1 wherein R_1, R_2, R_3, R_4 and R_5 are each independently selected from the group consisting of hydrogen, halo, CF_3, OR^{20}, C_{1-3} alkyl, C_{2-3} alkenyl, or C_{2-3} alkynyl, wherein the alkyl is optionally substituted with CF_3;

R_6, R_7 and R_8 each independently selected from the group consisting of hydrogen or methyl;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group consisting of hydrogen or C_{1-2} alkyl, wherein R^9 and R^{10} may together form a carbonyl, or R^{11}

and R^{12} may together form a carbonyl, or R^{13} and R^{14} may together form a carbonyl, or R^{15} and R^{16} may together form a carbonyl;

R_{17}, R_{18}, R_{19}, R_{20}, and R_{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR_{23}, COR_{23}, CO_2R_{23}, $CON(R_{23})_2$, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl and aryl substituent are optionally substituted with 1 substituent selected from the group consisting of halo, CF_3, and OR_{23};

R_{22} is selected from the group consisting of C_{1-4} alkyl, aryl, or heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, alkyl, O-C_{1-3} alkyl, or CF_3; and

R_{23} is selected from the group consisting of H, C_{1-5} alkyl, aryl, or heteroaryl, wherein the alkyl and aryl substituents are optionally substituted with 1 substituent selected from the group consisting of halo, -OMe, or CF_3.

5. The compound of claim 1 wherein R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, halo, CF_3, OR^{22} and C_{1-4} alkyl wherein R^{22} is a member selected from the group consisting of C_{1-3} alkyl;

R^6, R^7 and R^8 each independently selected from the group consisting of hydrogen and C_{1-3} alkyl;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from hydrogen, C_{1-4} alkyl, or R^9 and R^{10} may together form a carbonyl, or R^{15} and R^{16} may together form a carbonyl or R^{10} and R^{11} may together form $-CH_2CH_2CH_2CH_2-$; and

R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, CN, OR^{22}, $S(O)R^{22}$, SO_2R^{22}, $SON(R^{22})_2$, $CON(R^{22})_2$, C_{1-4} alkyl, or R^{17} and R^{18} may together form -CH=CH-CH=CH-, or R^{18} and R^{19} may together form $-OCH_2O-$, wherein R^{22} is C_{1-3} alkyl.

6. The compound of claim 5 wherein X = -O-

7. The compound of claim 5 wherein is $(CH_2)_n$ wherein n = 0 or 1.

8. The compound of claim 5 wherein m is 0.

9. The compound of claim 5 wherein m is 1.

10. The compound of claim 5 wherein R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, OR^{22} and C_{1-4} alkyl wherein R^{22} is a member selected from the group consisting of C_{1-3} alkyl.

11. The compound of claim 5 wherein R^6, R^7 and R^8 each independently selected from the group consisting of hydrogen and methyl.

12. The compound of claim 5 wherein R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from hydrogen, and C_{1-3} alkyl.

13. The compound of claim 5 wherein R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, OR^{22}, C_{1-2} alkyl, or R^{18} and R^{19} may together form $-OCH_2O-$, wherein R^{22} is C_{1-2} alkyl.

14. The compound of claim 1 wherein R^1, R^2, R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, and C_{1-2} alkyl;

R^6, R^7 and R^8 are each hydrogen;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from hydrogen, ethyl and methyl; and

R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, halo, CF_3, OR^{22}, methyl, wherein R^{22} is methyl.

15. The compound of claim 14 wherein R^1 and R^5 are each methyl.

16. The compound of claim 14 wherein R^2, R^3, R^4, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each hydrogen.

17. The compound of claim 14 wherein R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen and halo.

18. A substituted piperazine compound of claim 1 selected from the group consisting of N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-3-phenylpropanoyl)piperazinyl]acetamide, N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-3-indol-3-ylpropanoyl)piperazinyl]acetamide, N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-4-phenylbutanoyl)piperazinyl]acetamide, N-(2,6-dimethylphenyl)-2-{4-[2-(2-chlorophenoxy)acetyl]piperazinyl}acetamide, N-(2,6-dimethylphenyl)-2-[4-(4-phenylbutanoyl)piperazinyl]acetamide, N-(2,6-dimethylphenyl)-2-[4-(3-phenylpropanoyl)piperazinyl]acetamide, N-(2,6-dimethylphenyl)-2-[4-(2-phenylacetyl)piperazinyl]acetamide, N-(2,6-dimethylphenyl)-2-[4-(2-hydroxy-3-indol-3-ylpropanoyl)piperazinyl]acetamide, and 2-[4-((2R)-2-hydroxy-4-phenylbutanoyl)piperazinyl]-N-(2,6-dimethylphenyl)acetamide.

19. A method of treatment comprising administering a therapeutically effective amount of a compound of claim 1 to a mammal in need of a treatment selected from the group consisting of protecting skeletal muscles against damage resulting from trauma, protecting skeletal muscles subsequent to muscle or systemic diseases, treating shock conditions, preserving donor tissue and organs used in transplants, or treating cardiovascular diseases.

20. The method of claim 19 wherein the cardiovascular disease is selected from the

group consisting of atrial and ventricular arrhythmias, Prinzmetal's (variant) angina, stable angina, exercise induced angina, congestive heart disease, or myocardial infarction.

21. The method of claim 19 wherein the therapeutically effective amount ranges from about 0.01 to about 100 mg/kg weight of the mammal.

22. The method of claim 19 wherein the mammal is a human.

23. A pharmaceutical composition of matter comprising the compound of claim 1 and one or more pharmaceutical excipients.

24. The pharmaceutical composition of matter of claim 23 wherein the pharmaceutical composition is in the form of a solution.

25. The pharmaceutical composition of matter of claim 23 wherein the pharmaceutical composition is in a form selected from the group consisting of a tablet or a capsule.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D295/18 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 262 521 A (DELALANDE SA) 26 September 1975 (1975-09-26) page 2; example ---	1,23
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 June 2001	04/07/2001

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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